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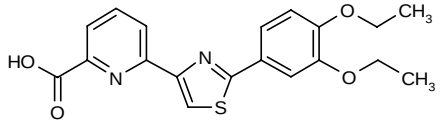
Tetomilast

Prop INN

Treatment of Inflammatory Bowel Disease
Treatment of COPD
Antioxidant
PDE4 Inhibitor

OPC-6535

6-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid



$C_{19}H_{18}N_2O_4S$
Mol wt: 370.43
CAS: 145739-56-6
EN: 186312

Abstract

Reactive oxygen species released by activated neutrophils are involved in the inflammatory response of tissues, and thus have a role in the pathogenesis of such diverse diseases as ulcerative colitis and chronic obstructive pulmonary disease (COPD), among others. Tetomilast inhibits superoxide production by human neutrophils, and also has phosphodiesterase type 4 (PDE4)-inhibitory activity. The protective effects of tetomilast have been demonstrated in a number of models, including sepsis-induced lung injury and myocardial ischemia/reperfusion-induced damage in pigs. Suppression of superoxide and TNF-α production from hepatic macrophages in rats was observed, and multiple inhibitory actions of tetomilast on leukocyte activation have been confirmed *in vitro*. The preliminary safety and efficacy of tetomilast have been demonstrated in mild to moderately active ulcerative colitis, with greater efficacy observed in patients with more severe disease at baseline. Tetomilast is in phase III clinical studies for ulcerative colitis, as well as phase II clinical trials for COPD.

Synthesis

Bromination of 6-acetylpyridine-2-carboxylic acid (I) in hot AcOH gives the α-bromoketone (II), which is subsequently esterified to compound (III) by refluxing in MeOH. Condensation of bromoketone (III) with 3,4-diethoxythiobenzamide (IV) – prepared by treatment of 3,4-diethoxybenzonitrile (V) with thioacetamide (VI) in the presence of HCl – in refuxing MeOH provides the thiazole derivative (VII), which is finally hydrolyzed under basic conditions (1-3). Scheme 1.

Alternatively, 3,4-diethoxythiobenzamide (IV) can be obtained by reaction of 1,2-diethoxybenzene (VIII) with KSCN in either aqueous 80% H_2SO_4, polyphosphoric acid, liquid HF or methanesulfonic acid (4), or by reaction of 3,4-diethoxybenzamide (IX) with P_2S_5 in refluxing benzene (3). Scheme 1.

Introduction

Neutrophils are known to play a central role in mediating tissue injury in inflammation, particularly due to the release of reactive oxygen species (ROS) such as superoxide upon activation by immune factors including cytokines. Ulcerative colitis is an inflammatory condition involving the inner lining of the colon and rectum. Inflammatory bowel diseases are characterized by an abnormal mucosal barrier function, whereby a loss of mucosal permeability may result in systemic and local inflammation and tissue injury, associated with high levels of reactive oxygen metabolites. Reactive oxygen species also participate in lung injury and multiple organ failure (5-9).

Approaches to preventing superoxide-induced injury consist of scavenging the superoxide or inhibiting its production. Tetomilast (OPC-6535) is a novel thiazole derivative that potently inhibits superoxide production by human neutrophils (IC_{50} = 0.07 μM) (1), and which has also been reported to inhibit phosphodiesterase type 4 (PDE4).

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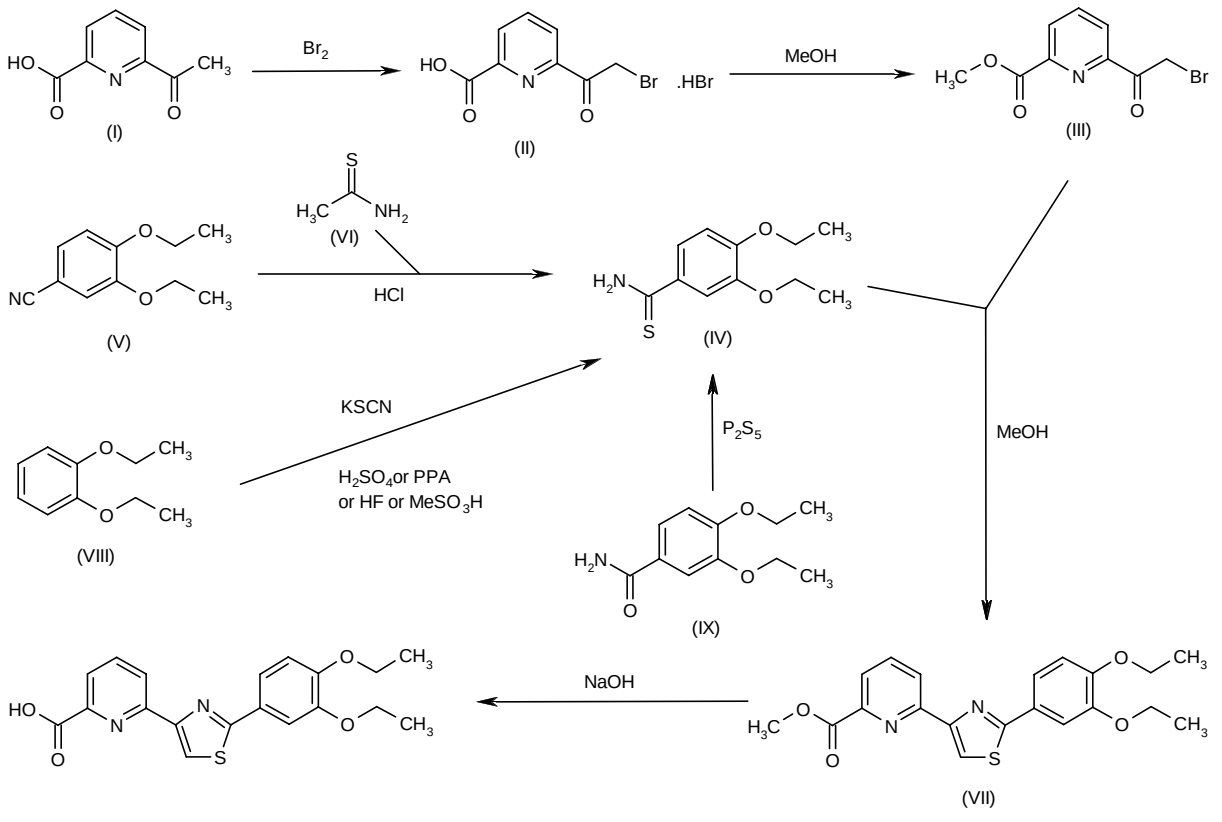
Scheme 1: Synthesis of Tetomilast



Pharmacological Actions

The effect of tetomilast on the cytoskeletal protein actin and mucosal barrier integrity was investigated in the human colon Caco-2 cell line. Cell monolayers were pretreated with tetomilast 10 μM prior to incubation with reactive oxygen metabolites. Actin cytoskeletal disruption and monolayer barrier dysfunction were prevented, as shown by inhibition of actin oxidation, decreased polymerized G-actin and enhanced stable F-actin. These data provided evidence that tetomilast directly protects the mucosal barrier from damage by oxidant insult, by preventing the oxidation, disassembly and instability of the cytoskeletal protein actin (10).

The protective effect of tetomilast was also evaluated in sepsis-induced lung injury in pigs. In this model, the lung injury induced is highly dependent upon neutrophil adhesion and extracellular release of ROS, which is also characteristic of damage in adult respiratory distress syndrome (ARDS). Pigs were treated with tetomilast (1 mg/kg by bolus infusion) prior to a bacterial infusion. These animals had significantly reduced acute lung injury compared with untreated septic animals, as demonstrated by a significant improvement in bronchoalveolar protein content and neutrophil count, and arterial oxygenation. Evidence that tetomilast interferes with oxidant production by neutrophils was provided by the observation that treated septic animals produced 25% less superoxide anion than untreated septic animals, although this decrease was not statistically significant (11).

The protective effect of tetomilast on myocardial ischemia/reperfusion damage was demonstrated in both pigs and rabbits. In pigs, tetomilast significantly and dose-dependently (30 and 60 μg/kg/min by 15-min i.v. infusion starting 20 min after occlusion) reduced myocardial infarct size after 5 h of reperfusion and significantly improved left ventricular function and reduced the extent of myocardial fibrosis after long-term reperfusion (4 weeks) (12-14). In an isolated working rabbit heart model of ischemia/reperfusion injury, improved ventricular function and a significant reduction in serum creatine kinase and lipid peroxidation were observed in the group treated with tetomilast (3 mg/kg) compared with the control group (15).

Administration of tetomilast before and after warm ischemia/reperfusion of liver grafts in a pig model resulted in a marked reduction in leukocyte accumulation and congestion. The reduced postoperative hyperbilirubinemia and low mortality indicated that the release of ROS may play a critical role in graft liver injury. The results of

this study indicated that tetomilast may have utility for protecting liver grafts from a non-heart-beating donor (16).

Protective effects of tetomilast were also demonstrated against lipopolysaccharide (LPS)-induced liver injury in rats. Tetomilast (1 mg/kg i.v.) was administered before LPS challenge and added (10 μmol/l) to the buffer in perfusion experiments. The antiinflammatory and tissue-protective effects of tetomilast were demonstrated by suppression of superoxide and TNF-α production from hepatic macrophages. In *in vivo* studies, tetomilast reduced concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), evidence of its ability to reduce acute liver damage (17).

Tetomilast exerts multiple inhibitory actions on leukocyte activation *in vitro*. In neutrophils incubated with tetomilast at concentrations of 0.001-100 μM prior to the addition of stimuli, superoxide production was inhibited in a concentration-dependent manner. Tetomilast also inhibited hydrogen peroxide production concentration-dependently in neutrophils and superoxide production in monocytes. Tetomilast inhibited neutrophil adhesion to cultured human umbilical vein endothelial cells (HUVEC). It also inhibited cytokine production in neutrophils, monocytes and human peripheral blood mononuclear cells (18-22).

The pharmacological effects of tetomilast on TNF-α production in leukocytes were examined *in vitro* and *in vivo*. In human whole blood and isolated human monocytes, tetomilast inhibited LPS-stimulated TNF-α production in a concentration-dependent manner, with respective IC_{50} values of 10 μM and 2.4 μM. In an *in vivo* porcine endotoxemia model, tetomilast (60 μg/kg/min by 15-min i.v. infusion) pretreatment significantly suppressed the LPS-stimulated increase in plasma TNF-α compared with vehicle controls (23).

The effects of tetomilast were evaluated in rat models of colitis. In colitis induced by rectal administration of TNBS, tetomilast was administered orally for 7 days at doses of 0.3, 1 and 3 mg/kg/day. There was a dose-related suppression of both the area of ulceration and the incidence of diarrhea, with maximum improvement observed at a dose of 1 mg/kg/day. At this dose, the clinical improvement was associated with inhibition of neutrophil infiltration into colonic tissue, and significant suppression of free radical and TNF-α production in the damaged tissue (24). In a rat model of DSS-induced chronic colitis, tetomilast (1 mg/kg/day) was administered orally for 4 weeks. The area of colonic erosion and symptoms of chronic colitis were significantly reduced in the tetomilast-treated group compared with vehicle controls (25).

Clinical Studies

The safety and efficacy of tetomilast in the treatment of mild to moderate active ulcerative colitis were assessed in a randomized, double-blind, placebo-controlled phase II study. A total of 186 patients received tetomilast 25 or 50 mg p.o. or placebo once daily for 8 weeks. The mean improvement in the Disease Activity Index (DAI) was significantly greater in the 25-mg group and approached statistical significance in the 50-mg group compared with the placebo group. The reduction in rectal bleeding was also significantly greater in the low-dose group. However, a significantly higher proportion of patients in the high-dose group achieved remission. There was a greater improvement in the subgroup of patients with more severe disease (DAI = 7-11) at baseline, with or without concomitant use of 5-aminosalicylic acid (26-28).

Pivotal phase III studies of tetomilast in ulcerative colitis were initiated in the U.S., Canada and Australia in 2003, and phase II trials are under way in COPD (29, 30).

Sources

Otsuka America Pharmaceutical, Inc. (US); Otsuka Maryland Research Institute, Inc. (US); Otsuka Pharmaceutical Co. (JP).

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